REMARKS

All of the previously pending claims in the instant application have been cancelled without prejudice to Applicants right to pursue the subject matter of these claims in any related application. New claims 31 through 55 are submitted herewith in order to address the Examiner's rejection of the previous claims under 35 U.S.C. § 112 and to more particularly point that which Applicants regard as their elected invention. No new matter is added by this amendment; entry of these new claims is respectfully requested. Support for the amended claims may be found, *inter alia*, in the specification as filed at Figures 1, 2 and 3; and at pages 29, 31-32, 34 and 40.

The specification has been amended in order to correct minor typographical errors and to fully comply with the guidelines governing sequence listings. Specifically, the brief description of the figures has been amended to refer to the sequences in Figures 9-11 by their sequence identifiers.

1. The Invention.

The present invention relates to novel nonreceptor tyrosine kinases, referred to as MKK1, MKK2 and MKK3. As described in the instant specification, the nonreceptor tyrosine kinases of the invention are expressed in megakaryocytes and are involved in signal transduction pathways.

In addition to tyrosine kinase domains, the MKK polypeptides of the invention contain the functional domains SH2 and SH3, which are known to be involved in mediating protein-protein interactions. Specifically, SH2 domains bind phosphotyrosine-containing amino acid sequences present in other proteins (e.g., tyrosine kinase molecules). SH3 domains also mediate protein-protein interactions by binding to SH3-binding domains present in other proteins (e.g., cytoskeletal proteins or G-proteins).

Further, the MKK2 of the claimed invention contains a pleckstrin homology (PH) domain, which has also been shown involved in protein-protein interactions. Because these functional domains act independently of each other, an MKK deleted for one of these domains, for example the SH3 domain, retains biological activity in that it retains significant ability to interact with other components of an MKK signal transduction pathway. As taught by the instant specification, MKKs and such functional derivatives of MKKs are useful in identifying compounds capable of modulating signal transduction. (*See* specification, page 31, line 31 to page 32, line 10).

The present invention, as claimed, specifically relates to isolated proteins containing at least 15 contiguous amino acid residues within the amino acid sequences depicted in SEQ ID NOS:2, 4 and 6.

2. The Claims Have Been Amended To Comply With The Sequence Rules.

The Examiner has objected to Claims 15, 17 and 19 as not complying with § 1.821(d) of the Sequence Rules and Regulations. Specifically, these claims referred to sequences by their figure numbers instead of their sequence identifiers. Applicants have cancelled these claims and submit new claims which obviate this rejection. Specifically, new Claims 31 to 55 refer to MKK sequences by their sequence or sequence identifiers. Withdrawal of this objection is respectfully requested.

3. The Rejection Under 35 U.S.C. §112 For Lack of Enablement Is Improper.

The Claims are rejected under 35 U.S.C. § 112, first paragraph, as the Examiner asserts that the specification does not enable all polypeptides encompassed by the names "MKK1", "MKK2", and "MKK3". The Examiner alleges that the name or abbreviation for a protein is subject to change, and other authors have referred to megakaryocytic

kinases by other names. Additionally, the Examiner asserts that although generation of mutants is within the skill of the artisan, there is insufficient guidance in the specification to obtain MKK mutants with functional activity.

This rejection is overcome and/or obviated by the amended claims which define the MKK polypeptides of the claimed invention by reference to the amino acid sequences disclosed in the specification, as suggested by the Examiner. In particular, new Claims 31-39, 41-47, and 49-54 are directed towards amino acid sequences presented in SEQ ID NOS:2, 4 and 6. New Claims 40, 48 and 55 are directed only to those MKK polypeptides encoded by naturally occurring nucleic acid molecules that hybridize under highly stringent conditions to the nucleic acid sequence which encodes the MKK polypeptide of SEQ ID NOS 2, 4 and 6, respectively.

Applicants maintain that the presently pending new claims are not so broad as to encompass any and all mutants, and instead encompass only the MKK polypeptide sequences specified, or naturally occurring MKK polypeptides in other cell types and species. In view of the well known degeneracy of the genetic code, one skilled in the art would readily be able to ascertain nucleotide sequences that encode the amino acid sequence specified in Claim 31, 41 and 49. Similarly, one skilled in the art would readily be able to retrieve DNA sequences encoding naturally occurring MKK polypeptides from other species or cell types using standard hybridization techniques. As taught in the instant specification by way of working examples, such DNA sequences may be used to produce the MKK polypeptides of the claimed invention.

In light of these amendments and the discussion presented above, Applicants respectfully request reconsideration and withdrawal of the rejections under 33 U.S.C. § 112.

4. Bennett and Lee Cannot Be Considered Prior Art For Any Purposes Under 35 U.S.C. §§ 102(a) or 103.

Claims 14 and 15 covering MKK1 polypeptides are rejected under 35 U.S.C. § 102(a) as anticipated by Bennett *et al.* ("Bennett").

Claims 18 and 19 covering MKK3 polypeptides are rejected under 35 U.S.C. § 103 as obvious over Lee *et al.* ("Lee") combined with Sambrook *et al.* ("Sambrook").

Although new Claims 31-40 and 49-55 have not been rejected, the new claims cover MKK1 and MKK3 polypeptides; therefore, this rejection is addressed below.

Assuming arguendo that the subject matter of any of the references did indeed anticipate or make obvious the MKK polypeptides of the claimed invention, Applicants contend that neither reference is available as prior art. To support their contention, Applicants provide the accompanying faxed copy of a Declaration by the Inventors under 37 C.F.R. § 131, signed by Dr. Ullrich, Dr. Gishizky and Dr. Sures. The original copy of this declaration will be forwarded to the Patent Office after it is received by Attorneys for Applicants. This declaration is evidence that prior to the effective date of Bennett, which was published January 14, 1994, the Applicants had conceived of the invention and were duly diligent in reducing it to practice and/or actually reduced it to practice in the United States by expressing and isolating MKK1 polypeptide.

Applicants also submit a duplicate copy of a Declaration by the Inventors under 37 C.F.R. § 1.131, which was filed in copending U.S. application serial no. 08/232,545. This declaration is evidence that, prior to the January 28, 1994 publication date of Lee, the Applicants had conceived of the invention and were duly diligent in reducing it to practice and/or actually reduced it to practice in the United States by introducing the complete coding sequence of human MKK3, as well as a cloned plasmid containing the isolated polynucleotide encoding MKK3. Thus, prior to the effective date of Lee,

Applicants have shown completion of the claimed invention commensurate in scope with the extent the invention is allegedly shown in Lee.

In view of these declarations, Bennett and Lee cannot be considered prior art under 35 U.S.C. §§ 102(a) and 103, respectively.

5. The Claims Are Not Obvious Under 35 U.S.C. §103 Over Cance et al. In Combination With The Secondary Reference.

5.1 The Partial Amino Acid Sequence Disclosed By Cance (1993) In View of Sambrook Does Not Render Obvious The Claimed MKK3 Polypeptides.

Claims 18 and 19 are rejected under 35 U.S.C. §103 as obvious over Cance *et al.* ("Cance"). Cance disclose a partial amino acid sequence encoding *TK1*, a protein tyrosine kinase expressed at high levels in breast cell lines. A comparison of the partial *TK1* amino acid sequence with the complete sequence of MKK3 suggests that the partial amino acid sequence of *TK1* may be similar to the corresponding region of MKK3. The Examiner claims that it would have been obvious to the skilled artisan at the time to use the partial cDNA of Cance as a probe to screen a BT20 cDNA library with the expectation of isolating the full length TK1 cDNA. The Examiner further asserts that it would be obvious to subclone the isolated full length cDNA into an expression vector, and to transfect the vector into a host cell for the production of large quantities of protein as taught by Sambrook. The Examiner claims that the motivation to isolate the full length cDNA is the teaching of Cance that src kinases may play an important role in the pathogenesis of cell cycles. This rejection is in error and should be withdrawn for reasons detailed below.

When, as here, a new chemical entity is claimed in structural terms, "a *prima facie* case of unpatentability requires that the teachings of the prior art suggest *the claimed*

compounds to a person of ordinary skill in the art." *In re Deuel*, 51 F.3d 1552, 1557 (Fed. Cir. 1995).

In the instant application, the claimed compounds are MKK3 polypeptides. Cance only discloses a partial amino acid sequence. The partial amino acid sequence of Cance simply does not suggest the claimed MKK polypeptides. Further, the Examiner asserts that it would be obvious to use the nucleotides encoding this partial amino acid sequence as a probe; however, Cance does not even disclose the nucleotides encoding this partial amino acid sequence. Applicants respectfully submit that Cance cannot suggest the use of nucleotides which it does not even disclose.

In fact, the facts in the present case are analogous to the situation presented in *Deuel*. In *Deuel*, the Federal Circuit reversed a Board determination of *prima facie* obviousness and ruled that a reference disclosing a partial amino acid sequence of a protein does not suggest the DNA encoding the complete protein. Similarly, the partial amino acid sequence of Cance cannot suggest the complete structure of a protein. The claimed compounds are not suggested by Cance, since the specific compounds were not even envisioned by Cance.

The partial amino acid sequence of Cance does not even suggest the correct nucleotide sequence which the Examiner asserts would be obvious to use. "[B]ecause of the degeneracy of the genetic code, there are a vast number of nucleotide sequences that might code for a specific protein." *In re Bell*, 26 USPQ 2d 1529, 1531 (Fed. Cir. 1993). When a reference discloses an amino acid sequence which could be encoded by a large number of possible nucleic acid sequences, and does not suggest which of those possibilities are correct, the correct nucleic acid sequence is not obvious. *Id.* In *Bell*, it was undisputed that the amino acid sequence of the prior art could have been encoded by 10^{36} different nucleic acid sequences. In the instant case, due to the degeneracy of the

genetic code, the partial amino acid sequence of Cance could be encoded by on the order of 10^{28} different nucleic acid sequences. Therefore, since there is no suggestion in Cance as to which possible nucleic acid sequence is the correct sequence, the partial amino acid sequence of Cance does not render obvious the correct partial nucleic acid sequence.

In essence, the rejection is based upon the allegation that it would be obvious to take the partial amino acid sequence of Cance, construct a DNA probe (which is not disclosed by Cance) based upon the partial amino acid sequence, use the undefined probe to probe a cDNA library, isolate an undefined full length cDNA clone, subclone that undefined full length clone into an expression vector, recombinantly produce protein using the subclone, and purify that protein. Applicants submit that, as in *Deuel*, the Examiner has "improperly rejected the claims based on the alleged obviousness of a method of making the molecules."

Furthermore, Applicants traverse the Examiner's assertion that Cance provides motivation to isolate the full length protein in that this reference teaches that src kinases may play an important role in the pathogenesis of cell cycles. Applicants submit that this assertion is mere speculation and impermissible hindsight reconstruction of the claimed invention. "A general motivation to search for some gene that exists does not necessarily make obvious a specifically defined gene that is subsequently obtained as a result of that search. More is needed and it is not found here." *Deuel*, 51 F.3d at 1558. Therefore, simply asserting that a protein exhibits interesting properties does not constitute sufficient motivation to make the amino acid sequence of the protein obvious.

Applicants respectfully submit that, as in *Deuel*, the Examiner has not established a *prima facie* case of unpatentability. Applicants request reconsideration and withdrawal of this rejection.

5.2 Claim 22 Is Not Obvious Over Cance In View of Maniatis *et al.*

Claim 22, directed towards an MKK3 fusion protein, has been rejected as unpatentable over Cance in view of Maniatis *et al.* ("Maniatis"). The Examiner asserts that it would be obvious to modify the partial TK1 protein of Cance by fusing it to a heterologous protein following the method of Maniatis for production of fusion proteins using vectors suitable for expression of fused eukaryotic proteins. The Examiner asserts the motivation to obtain TK1 fusion proteins is provided by Maniatis who discloses the advantages of fusion proteins. This rejection is in error and should be withdrawn because (1) Cance in view of Maniatis does not disclose or suggest the polypeptides of the presently claimed invention; and (2) Cance in view of Maniatis does not enable the production of any fusion protein.

As discussed more fully above, Cance only discloses a partial amino acid sequence. This partial amino acid sequence does not suggest the claimed polypeptides since the specific polypeptides were not even envisioned by Cance. Nor does Maniatis provide any of the information which is lacking in Cance. Thus, under *Deuel*, Cance in combination with Maniatis does not suggest the instantly claimed MKK3 polypeptides.

Furthermore, with respect to printed publications cited to support a rejections under 35 U.S.C. § 103, these references must be enabling, thus placing the allegedly disclosed matter in the possession of the public. Applicants respectfully submit that Cance in combination with Maniatis does not enable production of MKK1 fused to a heterologous protein. Specifically, the method of Maniatis requires that one possess the cloned DNA sequence encoding the polypeptide of interest. However, as noted above, Cance does not describe the full length nucleotide sequence or amino acid sequence of MKK1. Further, Cance does not actually disclose any polynucleotide sequence information for TK1. Therefore, because Cance does not provide crucial amino acid and

nucleic acid sequence information, Cance in view of Maniatis does not enable the claimed invention.

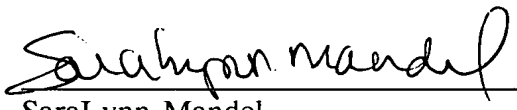
In light of the above remarks, Applicants submits that Cance in combination with Maniatis does not render obvious the claimed invention and respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 103.

CONCLUSION

Entry of the foregoing remarks into the file of the above specified application is respectfully requested. Applicants believe that each ground for rejection and objection has been successfully overcome or obviated and that the claims are in condition for allowance. Withdrawal of all the Examiner's rejections and objections is requested and an early allowance is earnestly sought. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

Date November 12, 1996



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